5.0 Inhalation Health Benchmarks

Chronic inhalation health benchmarks used in IWAIR include RfCs to evaluate noncancer risk from inhalation exposures, and inhalation CSFs to evaluate risk for carcinogens. Inhalation CSFs are used in the model for carcinogenic constituents, regardless of the availability of an RfC. A majority of inhalation health benchmarks were identified in IRIS and HEAST (U.S. EPA, 1997b, 2001a). IRIS and HEAST are maintained by EPA, and values from IRIS and HEAST were used in the model whenever available. Benchmarks from Superfund Risk Assessment Issue Papers, provisional EPA benchmarks, and benchmarks derived by the Agency for Toxic Substances and Disease Registry (ATSDR) and the California Environmental Protection Agency (CalEPA) were also used.

This section presents the noncancer and cancer inhalation benchmarks used in IWAIR. Section 5.1 describes the different types of human health benchmarks used in IWAIR; Sections 5.2 and 5.3 discuss data sources and the hierarchy used to select benchmarks for inclusion in IWAIR; and Section 5.4 provides the inhalation health benchmarks included in IWAIR for each constituent.

IWAIR provides at least one health benchmark for all chemicals included in its database except 3,4-dimethylphenol and divalent mercury. Users may override the IWAIR values with their own values. In this way, users can include new information that becomes available on health benchmarks after IWAIR is released.

5.1 Background

A chemical's ability to cause an adverse health effect depends on the toxicity of the chemical, the chemical's route of exposure to an individual (either through inhalation or ingestion), the duration of exposure, and the dose received (the amount that a human inhales or ingests). The toxicity of a constituent is defined by a human health benchmark for each route of exposure. Essentially, a benchmark is a quantitative value used to predict a chemical's possible toxicity and ability to induce a health effect at certain levels of exposure. These health benchmarks are derived from toxicity data based on animal studies or human epidemiological studies. Each benchmark represents a dose-response estimate that relates the likelihood and severity of adverse health effects to exposure and dose. Because individual chemicals cause different health effects at different doses, benchmarks are chemical-specific.

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is unlikely to pose an appreciable risk of deleterious noncancer effects during an individual's lifetime. It is not a direct estimator of risk but rather a reference point to gauge the potential effects. At exposures

increasingly greater than the RfC, the potential for adverse health effects increases. Lifetime exposure above the RfC does not imply that an adverse health effect would necessarily occur (U.S. EPA, 2001a).

The RfC is the primary benchmark used to evaluate noncarcinogenic hazards posed by inhalation exposures to chemicals. It is based on the "threshold" approach, which is the theory that there is a "safe" exposure level (i.e., a threshold) that must be exceeded before an adverse noncancer effect occurs. RfCs do not provide true dose-response information in that they are estimates of an exposure level or concentration that is believed to be below the threshold level or no-observed-adverse-effects level (NOAEL). The degree of uncertainty and confidence levels in RfCs vary and are based on different toxic effects.

The CSF is an upper-bound estimate (approximating a 95 percent confidence limit) of the increased human cancer risk from a lifetime exposure to an agent. This estimate is usually expressed in units of proportion (of a population) affected per mg of agent per kg body weight per day $(mg/kg\text{-}d)^{-1}$. The unit risk factor (URF), which is calculated from the slope factor, is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. That is, if the unit risk factor equals 1.5E–6 $(\mu g/m^3)^{-1}$, then 1.5 excess tumors are expected to develop per 1,000,000 people if they are exposed to 1 µg of the chemical in 1 m^3 of air daily for a lifetime (U.S. EPA, 2001a). Unlike RfCs, CSFs and URFs do not represent "safe" exposure levels; rather, they describe the relationship between level of exposure and probability of effect or risk.

5.2 Data Sources

Human health benchmarks were obtained primarily from IRIS, EPA's electronic database containing information on human health effects (U.S. EPA, 2001a), and from HEAST, a comprehensive listing of provisional noncarcinogenic and carcinogenic health toxicity values derived by EPA (U.S. EPA, 1997b). These sources and others used are described below. Inhalation CSFs are not available from IRIS (with the exception of benzidene) and are often not available from other sources, so they were calculated from inhalation URFs (which are available from IRIS), using the following equation (U.S. EPA, 1997b):

$$CSF_{inh} = \frac{URF_{inh} \times BW \times 1000}{IR} \qquad (5\text{-}1)$$

where

CSF_{inh} = inhalation cancer slope factor $(mg/kg\text{-}d)^{-1}$
URF_{inh} = inhalation unit risk factor $(\mu g/m^3)^{-1}$
BW = body weight (kg) = 70 kg
1000 = unit conversion (µg/mg)
IR = inhalation rate (m^3/day) = 20 m^3/day

The body weight and inhalation rate used in this equation are averages; because these standard estimates of body weight and inhalation rate are used by EPA in the calculation of URFs, these values are needed to convert inhalation URFs to inhalation CSFs.

The following sections describe each of the data sources used.

5.2.1 IRIS

Benchmarks in IRIS are prepared and maintained by EPA, and values from IRIS were used in IWAIR whenever available. Each chemical file in IRIS contains descriptive and quantitative information on potential health effects. Health benchmarks for chronic noncarcinogenic health effects include reference doses (RfDs) and RfCs. Cancer classification, oral CSFs, and inhalation URFs are included for carcinogenic effects. IRIS is the official repository of Agency-wide consensus information on human health toxicity benchmarks for use in risk assessments.

5.2.2 Superfund Technical Support Center

The Superfund Technical Support Center (EPA's National Center for Environmental Assessment (NCEA)) derives provisional RfCs, RfDs, and CSFs for certain chemicals. These provisional health benchmarks can be found in Risk Assessment Issue Papers. Some of the provisional values have been externally peer reviewed. The provisional health benchmarks have not undergone EPA's formal review process for finalizing benchmarks and do not represent Agency-wide consensus information.

A health benchmark developed by EPA is considered "provisional" if the value has had some form of Agency review but does not represent Agency-wide consensus (i.e., it does not appear on IRIS). At the time each provisional health benchmark was derived, all available toxicological information was evaluated, the value was calculated using the most current methodology, and a consensus was reached on the value by an individual EPA program office (but not Agency-wide) (U.S. EPA, 1997b). All health benchmarks not identified from IRIS, including minimum risk levels (MRLs) and CalEPA cancer potency factors and reference exposure levels (RELs), were treated as provisional health benchmarks.

5.2.3 HEAST

HEAST is a comprehensive listing of provisional noncarcinogenic and carcinogenic health toxicity values (RfDs, RfCs, URFs, and CSFs) derived by EPA (U.S. EPA, 1997b). HEAST benchmarks are considered secondary to those contained in IRIS. Although the health toxicity values in HEAST have undergone review and have the concurrence of individual EPA program offices, either they have not been reviewed as extensively as those in IRIS or their data set is not complete enough for the values to be listed in IRIS. HEAST benchmarks have not been updated in several years and do not represent Agency-wide consensus information.

5.2.4 Other EPA Documents

EPA has also derived health benchmark values that are reported in other risk assessment documents, such as Health Assessment Documents (HADs), Health Effect Assessments (HEAs), Health and Environmental Effects Profiles (HEEPs), Health and Environmental Effects Documents (HEEDs), Drinking Water Criteria Documents, and Ambient Water Quality Criteria Documents. Evaluations of potential carcinogenicity of chemicals in support of reportable quantity adjustments were published by EPA's Carcinogen Assessment Group (CAG) and may include cancer potency factor estimates. Health toxicity values identified in these EPA documents are usually dated and are not recognized as Agency-wide consensus information or verified benchmarks.

5.2.5 ATSDR

ATSDR calculates MRLs that are substance-specific health guidance levels for noncarcinogenic endpoints. An MRL is an estimate of the daily human exposure to a hazardous substance that is unlikely to pose an appreciable risk of adverse noncancer health effects over a specified exposure duration. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. MRLs are derived for acute, intermediate, and chronic exposure durations for oral and inhalation routes of exposure. Inhalation and oral MRLs are derived in a manner similar to EPA's RfCs and RfDs, respectively (i.e., ATSDR uses the NOAEL/uncertainty factor (UF) approach); however, MRLs are intended to serve as screening levels and are exposure-duration-specific. Also, ATSDR uses EPA's 1994 inhalation dosimetry methodology (U.S. EPA, 1994b) in the derivation of inhalation MRLs.

5.2.6 CalEPA

CalEPA has developed cancer potency factors for chemicals regulated under California's Hot Spots Air Toxics Program (CalEPA, 1999a). The cancer potency factors are analogous to EPA's oral and inhalation CSFs. CalEPA has also developed chronic inhalation RELs, analogous to EPA's RfC, for 120 substances (CalEPA, 1999b, 2000). CalEPA used EPA's 1994 inhalation dosimetry methodology in the derivation of inhalation RELs. The cancer potency factors and inhalation RELs have undergone internal peer review by various California agencies and have been the subject of public comment.

5.3 Hierarchy Used

Different benchmarks from more than one of the above sources may be available for some chemicals. EPA established a hierarchy for the data sources to determine which benchmark would be used when more than one was available. In establishing this hierarchy, EPA sources were preferred over non-EPA sources, and among EPA sources, those reflecting greater consensus and review were preferred.

Because IRIS is EPA's official repository of Agency-wide consensus human health risk information, benchmarks from IRIS were used whenever available. Benchmarks from the Superfund Technical Support Center and HEAST were used if none were available from IRIS. If

health benchmarks were not available from IRIS, the Superfund Technical Support Center, or HEAST, benchmarks from alternative sources were sought. Benchmarks were selected from sources in the following order of preference:

- IRIS
- Superfund Technical Support Center Provisional Benchmarks
- HEAST
- ATSDR MRLs
- CalEPA chronic inhalation RELs and cancer potency factors
- EPA health assessment documents
- Various other EPA health benchmark sources.

5.4 Chronic Inhalation Health Benchmarks Included in IWAIR

The chronic inhalation health benchmarks used in IWAIR are summarized in Table 5-1. The CAS number, constituent name, RfC (in units of mg/m^3), noncancer target organs, inhalation CSF $(mg/kg\text{-}d)^{-1}$, inhalation URF $(\mu g/m^3)^{-1}$, and reference for each benchmark are provided in this table. "RfC target organ or critical effect" refers to the target organ (e.g., kidney, liver) or critical effect used as the basis for the RfC. The critical effect for a few benchmarks is listed as "no effect" and refers to the fact that no adverse effects were observed in the principal study. For acetonitrile, the RfC was based on increased mortality at higher dosage levels; therefore, the target organ was classified as "death." A key to the references cited and abbreviations used is provided at the end of the table.

For a majority of IWAIR constituents, human health benchmarks were available from IRIS (U.S. EPA, 2001a), Superfund Risk Issue Papers, or HEAST (U.S. EPA, 1997b). Benchmarks also were obtained from ATSDR (2001) or CalEPA (1999a, 1999b, 2000). In most cases, the benchmarks were taken directly from the cited source. This section describes the exceptions, in which benchmarks were adapted from the cited source.

- The cancer risk estimates for **benzene** are provided as ranges in IRIS. The inhalation URF for benzene is 2.2E−6 to 7.8E−6 $(\mu g/m^3)^{-1}$ (U.S. EPA, 2001a). For IWAIR, the upper-range estimate was used (i.e., 7.8E−6 $(\mu g/m^3)^{-1}$ for the inhalation URF).

- Based on use of the linearized multistage model, an inhalation URF of 4.4E−6 per $\mu g/m^3$ was recommended for **vinyl chloride** in IRIS and was used for IWAIR to account for continuous, lifetime exposure during adulthood; an inhalation CSF of 1.5E−2 per mg/kg-d was calculated from the URF.

- The benchmarks for 1,3-dichloropropene were used as surrogate data for **cis-1,3-dichloropropylene** and **trans-1,3-dichloropropylene**. The studies cited in the IRIS file for 1,3-dichloropropene used a technical-grade chemical that contained about a 50/50 mixture of the cis- and trans-isomers. The RfC is 2E−2 mg/m^3. The inhalation URF for 1,3-dichloropropene is 4E−6 $(\mu g/m^3)^{-1}$ (U.S. EPA, 2001a).

Table 5-1. Chronic Inhalation Health Benchmarks Used in IWAIR

Name	CAS No.	RfC (mg/m^3)	RfC Ref	RfC Target Organ or Critical Effect	URF $(\mu g/m3)^{-1}$	URF Ref	CSFi $(mg/kg\text{-}d)^{-1}$	CSFi Ref
Acetaldehyde	75-07-0	9.0E-03	I	Respiratory	2.2E-06	I	7.7E-03	calc
Acetone	67-64-1	3.1E+01	A	Neurological				
Acetonitrile	75-05-8	6.0E-02	I	Death				
Acrolein	107-02-8	2.0E-05	I	Respiratory				
Acrylamide	79-06-1				1.3E-03	I	4.6E+00	calc
Acrylic acid	79-10-7	1.0E-03	I	Respiratory				
Acrylonitrile	107-13-1	2.0E-03	I	Respiratory	6.8E-05	I	2.4E-01	calc
Allyl chloride	107-05-1	1.0E-03	I	Neurotoxicity	6.0E-06	C99a	2.1E-02	calc
Aniline	62-53-3	1.0E-03	I	Spleen	1.6E-06	C99a	5.6E-03	calc
Benzene	71-43-2	6.0E-02	C00	Hematological, developmental, neurological	7.8E-06	I	2.7E-02	calc
Benzidine	92-87-5				6.7E-02	I	2.3E+02	I
Benzo(a)pyrene	50-32-8				1.1E-03	C99a	3.9E+00	calc
Bromodichloromethane	75-27-4				1.8E-05	AC	6.2E-02	AC
Butadiene, 1,3-	106-99-0	2.0E-02	C00	Reproductive	2.8E-04	I	9.8E-01	calc
Carbon disulfide	75-15-0	7.0E-01	I	Neurological				
Carbon tetrachloride	56-23-5	7.0E-03	SF	Liver	1.5E-05	I	5.3E-02	calc
Chlorobenzene	108-90-7	6.0E-02	SF	Liver				
Chlorodibromomethane	124-48-1				2.4E-05	AC	8.4E-02	AC
Chloroform	67-66-3	1.0E-01	A	Liver				
Chlorophenol, 2-	95-57-8	1.4E-03	AC	Reproductive, developmental				
Chloroprene	126-99-8	7.0E-03	H	Respiratory				
Cresols (total)	1319-77-3	6.0E-01	C00	Neurological				
Cumene	98-82-8	4.0E-01	I	Adrenal, kidney				
Cyclohexanol	108-93-0	2.0E-05	solv	NA				
Dibromo-3-chloropropane, 1,2-	96-12-8	2.0E-04	I	Reproductive	6.9E-07	H	2.4E-03	calc
Dichlorodifluoromethane	75-71-8	2.0E-01	H	Liver				
Dichloroethane, 1,2-	107-06-2	2.4E+00	A	Liver	2.6E-05	I	9.1E-02	calc
Dichloroethylene, 1,1-	75-35-4	7.0E-02	C00	Liver	5.0E-05	I	1.8E-01	calc

(continued)

Table 5-1. (continued)

Name	CAS No.	RfC (mg/m^3)	RfC Ref	RfC Target Organ or Critical Effect	URF $(\mu g/m3)^{-1}$	URF Ref	CSFi $(mg/kg\text{-}d)^{-1}$	CSFi Ref
Dichloropropane, 1,2-	78-87-5	4.0E-03	I	Respiratory				
Dichloropropylene, cis-1,3-	10061-01-5	2.0E-02	surr	Respiratory	4.0E-06	surr	1.4E-02	calc
Dichloropropylene, trans-1,3-	10061-02-6	2.0E-02	surr	Respiratory	4.0E-06	surr	1.4E-02	calc
Dimethylbenz[a]anthracene, 7,12-	57-97-6				7.1E-02	C99a	2.5E+02	calc
Dimethylphenol, 3,4-	95-65-8							
Dinitrotoluene, 2,4-	121-14-2				8.9E-05	C99a	3.1E-01	calc
Dioxane, 1,4-	123-91-1	3.0E+00	C00	Liver, kidney, hematological	7.7E-06	C99a	2.7E-02	calc
Diphenylhydrazine, 1,2-	122-66-7				2.2E-04	I	7.7E-01	calc
Epichlorohydrin	106-89-8	1.0E-03	I	Respiratory	1.2E-06	I	4.2E-03	calc
Epoxybutane, 1,2-	106-88-7	2.0E-02	I	Respiratory				
Ethoxyethanol acetate, 2-	111-15-9	3.0E-01	C00	Developmental				
Ethoxyethanol, 2-	110-80-5	2.0E-01	I	Hematological, reproductive				
Ethylbenzene	100-41-4	1.0E+00	I	Developmental	1.1E-06	SF	3.9E-03	calc
Ethylene dibromide	106-93-4	2.0E-04	H	Reproductive	2.2E-04	I	7.7E-01	calc
Ethylene glycol	107-21-1	4.0E-01	C00	Respiratory, kidney, developmental				
Ethylene oxide	75-21-8	3.0E-02	C00	Neurological	1.0E-04	H	3.5E-01	calc
Formaldehyde	50-00-0	9.8E-03	A	Respiratory	1.3E-05	I	4.6E-02	calc
Furfural	98-01-1	5.0E-02	H	Respiratory				
Hexachloro-1,3-butadiene	87-68-3				2.2E-05	I	7.7E-02	calc
Hexachlorobenzene	118-74-1				4.6E-04	I	1.6E+00	calc
Hexachlorocyclopentadiene	77-47-4	2.0E-04	I	Respiratory				
Hexachloroethane	67-72-1				4.0E-06	I	1.4E-02	calc
Isophorone	78-59-1	2.0E+00	C99b	Developmental, kidney, liver				
Mercury (elemental)	7439-97-6	3.0E-04	I	Neurotoxicity				
Methanol	67-56-1	4.0E+00	C00	Developmental				
Methoxyethanol acetate, 2-	110-49-6	9.0E-02	C00	Reproductive				
Methoxyethanol, 2-	109-86-4	2.0E-02	I	Reproductive				

(continued)

Table 5-1. (continued)

Name	CAS No.	RfC (mg/m^3)	RfC Ref	RfC Target Organ or Critical Effect	URF $(\mu g/m3)^{-1}$	URF Ref	CSFi $(mg/kg\text{-}d)^{-1}$	CSFi Ref
Methyl bromide	74-83-9	5.0E-03	I	Respiratory				
Methyl chloride	74-87-3	9.0E-02	I	Neurological	1.8E-06	H	6.3E-03	calc
Methyl ethyl ketone	78-93-3	1.0E+00	I	Developmental				
Methyl isobutyl ketone	108-10-1	8.0E-02	H	Liver, kidney				
Methyl methacrylate	80-62-6	7.0E-01	I	Respiratory				
Methyl tert-butyl ether	1634-04-4	3.0E+00	I	Kidney, liver, eye				
Methylcholanthrene, 3-	56-49-5				6.3E-03	C99a	2.2E+01	calc
Methylene chloride	75-09-2	3.0E+00	H	Liver	4.7E-07	I	1.6E-03	calc
N,N-Dimethyl formamide	68-12-2	3.0E-02	I	Liver				
Naphthalene	91-20-3	3.0E-03	I	Respiratory				
n-Hexane	110-54-3	2.0E-01	I	Neurotoxicity, respiratory				
Nitrobenzene	98-95-3	2.0E-03	H	Adrenal, hematological, kidney, liver				
Nitropropane, 2-	79-46-9	2.0E-02	I	Liver	2.7E-03	H	9.5E+00	calc
N-Nitrosodiethylamine	55-18-5				4.3E-02	I	1.5E+02	calc
N-Nitrosodi-n-butylamine	924-16-3				1.6E-03	I	5.6E+00	calc
N-Nitrosopyrrolidine	930-55-2				6.1E-04	I	2.1E+00	calc
o-Dichlorobenzene	95-50-1	2.0E-01	H	Body weight				
o-Toluidine	95-53-4				6.9E-05	AC	2.4E-01	AC
p-Dichlorobenzene	106-46-7	8.0E-01	I	Liver	1.1E-05	C99a	3.9E-02	calc
Phenol	108-95-2	2.0E-01	C00	Liver, cardiovascular, kidney, neurological				
Phthalic anhydride	85-44-9	1.2E-01	H	Respiratory				
Propylene oxide	75-56-9	3.0E-02	I	Respiratory	3.7E-06	I	1.3E-02	calc
Pyridine	110-86-1	7.0E-03	EPA86	Liver				
Styrene	100-42-5	1.0E+00	I	Neurotoxicity				
TCDD, 2,3,7,8-	1746-01-6				3.3E+01	H	1.5E+05	H
Tetrachloroethane, 1,1,1,2-	630-20-6				7.4E-06	I	2.6E-02	calc

(continued)

Table 5-1. (continued)

Name	CAS No.	RfC (mg/m^3)	RfC Ref	RfC Target Organ or Critical Effect	URF $(\mu g/m3)^{-1}$	URF Ref	CSFi $(mg/kg\text{-}d)^{-1}$	CSFi Ref
Tetrachloroethane, 1,1,2,2-	79-34-5				5.8E-05	I	2.0E-01	calc
Tetrachloroethylene	127-18-4	3.0E-01	A	Neurological	5.8E-07	HAD	2.0E-03	HAD
Toluene	108-88-3	4.0E-01	I	Neurological, respiratory				
Tribromomethane	75-25-2				1.1E-06	I	3.9E-03	calc
Trichloro-1,2,2-trifluoroethane, 1,1,2-	76-13-1	3.0E+01	H	Body weight				
Trichlorobenzene, 1,2,4-	120-82-1	2.0E-01	H	Liver				
Trichloroethane, 1,1,1-	71-55-6	2.2E+00	SF	Neurological				
Trichloroethane, 1,1,2-	79-00-5				1.6E-05	I	5.6E-02	calc
Trichloroethylene	79-01-6	6.0E-01	C00	Neurological, eyes	1.7E-06	HAD	6.0E-03	HAD
Trichlorofluoromethane	75-69-4	7.0E-01	H	Kidney, respiratory				
Triethylamine	121-44-8	7.0E-03	I	Respiratory				
Vinyl acetate	108-05-4	2.0E-01	I	Respiratory				
Vinyl chloride	75-01-4	1.0E-01	I	Liver	4.4E-06	I	1.5E-02	calc
Xylenes	1330-20-7	4.0E-01	A	Neurological				

[a] Sources:
A = ATSDR MRLs (ATSDR, 2001)
AC = Developed for the Air Characteristic Study (U.S. EPA, 1999d)
C99a = CalEPA cancer potency factor (CalEPA, 1999a)
C99b = CalEPA chronic RELs (CalEPA, 1999b)
C00 = CalEPA chronic RELs (CalEPA, 2000)
I = IRIS (U.S. EPA, 2001a)
H = HEAST (U.S. EPA, 1997b)
HAD = Health Assessment Document (U.S. EPA, 1986a, 1987a)
SF = Superfund Risk Issue Paper (U.S. EPA, 1998a, 1999a,b,c)
solv = 63 FR 64371-0402 (U.S. EPA, 1998b)
surr = surrogate

[b] RfC and URF are for 1,3-dichloropropylene (U.S. EPA, 2001a)
[c] RfC is for total xylenes (ATSDR, 2001).

- A provisional subchronic RfC of 2E−2 mg/m^3 was developed by the Superfund Technical Support Center (U.S. EPA, 1999a) for **carbon tetrachloride**. A provisional chronic RfC of 7E−3 was derived by applying an uncertainty factor of 3 to account for the use of a subchronic study.

- An inhalation acceptable daily intake (ADI) of 2E−3 mg/kg-d based on an inhalation study was identified for **pyridine** (U.S. EPA, 1986b). An ADI is defined as "the amount of chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect." The units of an ADI (mg/kg-d) differ from those of an RfC (mg/m^3), illustrating that the inhalation ADI represents an internal dose, while an RfC represents an air concentration. In the U.S. EPA (1986b), EPA calculated the inhalation ADI by

  1. Using a lowest-observed-adverse-effect level (LOAEL) of 32.35 mg/m^3 (for increased liver weights observed in rats exposed to pyridine via inhalation)

  2. Assuming a rat breathes 0.223 m^3/day, absorbs 50 percent of the inhaled pyridine, and weighs 0.35 kg

  3. Converting from intermittent to continuous exposure by multiplying by 7/24 and 5/7.[1] (A "transformed dose" of 2.15 mg/kg-d results from these first three steps).

  4. Dividing the "transformed dose" of 2.15 mg/kg-d by an uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for human variability, and 10 for use of a LOAEL) (U.S. EPA, 1986b).

  The equation used in U.S. EPA (1986b) to calculate the inhalation ADI is as follows:

$$\text{inhalation ADI} = \frac{\text{LOAEL} \times \text{IR} \times 0.50 \times 5/7 \times 7/24}{\text{BW} \times 1000}$$

  where

  LOAEL = lowest-observed-adverse-effect level (mg/m^3) = 32.35
  IR = inhalation rate of rat (m^3/d) = 0.233
  BW = body weight of rat (kg) = 0.35.

[1] Rats were exposed to pyridine for 7 hours per day (instead of 24), 5 days per week (instead of 7).

For IWAIR, the inhalation ADI was converted to a provisional RfC of 7E−3 mg/m^3 by eliminating the parameters that were used to estimate an internal dose: rat inhalation rate, percent absorption, and rat body weight, thereby resulting in an air concentration suitable for use as a provisional RfC. The calculation is as follows:

$$\text{provisional RfC} = \frac{\text{LOAEL} \times 5/7 \times 7/24}{1000}$$

where

LOAEL = lowest-observed-adverse-effect level (mg/m^3) = 32.35.

Provisional inhalation health benchmarks were developed in the Air Characteristic Study (U.S. EPA, 1999d) for several constituents lacking IRIS, HEAST, alternative EPA, or ATSDR values. Those used for IWAIR are summarized in Table 5-2 below. Additional details on the derivation of these inhalation benchmarks can be found in the *Revised Risk Assessment for the Air Characteristic Study* (U.S. EPA, 1999d).

- A provisional RfC was developed in the Air Characteristic Study for **2-chlorophenol** using route-to-route extrapolation of the oral RfD.

- Based on oral CSFs from IRIS and HEAST, provisional inhalation URFs and inhalation CSFs were developed for **bromodichloromethane**, **chlorodibromomethane**, and **o-toluidine**.

Table 5-2. Provisional Inhalation Benchmarks Developed in the Air Characteristic Study

CAS No.	Chemical Name	RfC (mg/m^3)	RfC Target	Inh URF $(\mu g/m^3)^{-1}$	Inh CSF $(mg/kg\text{-}d)^{-1}$
75-27-4	Bromodichloromethane (dichlorobromomethane)			1.8E−5	6.2E−2
124-48-1	Chlorodibromomethane (dibromochloromethane)			2.4E−5	8.4E−2
95-57-8	2-Chlorophenol (o-)	1.4E−3	Reproductive, developmental		
95-53-4	o-Toluidine (2-methylaniline)			6.9E−5	2.4E−1

Finally, **chloroform** presents an unusual case. EPA has classified chloroform as a Group B2, Probable Human Carcinogen, based on an increased incidence of several tumor types in rats and mice (U.S. EPA, 2001a). However, based on an evaluation initiated by EPA's Office of Water (OW), the Office of Solid Waste (OSW) now believes the weight of evidence for the

carcinogenic mode of action for chloroform does not support a mutagenic mode of action; therefore, a nonlinear low-dose extrapolation is more appropriate for assessing risk from exposure to chloroform. EPA's Science Advisory Board (SAB), the World Health Organization (WHO), the Society of Toxicology, and EPA all strongly endorse the nonlinear approach for assessing risks from chloroform. Although OW conducted its evaluation of chloroform carcinogenicity for oral exposure, a nonlinear approach for low-dose extrapolation would apply to inhalation exposure to chloroform as well, because chloroform's mode of action is understood to be the same for both ingestion and inhalation exposures. Specifically, tumorigenesis for both ingestion and inhalation exposures is induced through cytotoxicity (cell death) produced by the oxidative generation of highly reactive metabolites (phosgene and hydrochloric acid), followed by regenerative cell proliferation (U.S. EPA, 1998c). Chloroform-induced liver tumors in mice have only been seen after bolus corn oil dosing and have not been observed following administration by other routes (i.e., drinking water and inhalation). As explained in EPA OW's March 31, 1998, and December 16, 1998, *Federal Register* notices pertaining to chloroform (U.S. EPA 1998c and 1998d, respectively), EPA now believes that "based on the current evidence for the mode of action by which chloroform may cause tumorigenesis, ... a nonlinear approach is more appropriate for extrapolating low dose cancer risk rather than the low dose linear approach..." (U.S. EPA 1998c). OW determined that, given chloroform's mode of carcinogenic action, liver toxicity (a noncancer health effect) actually "is a more sensitive effect of chloroform than the induction of tumors" and that protecting against liver toxicity "should be protective against carcinogenicity given that the putative mode of action ... for chloroform involves cytotoxicity as a key event preceding tumor development" (U.S. EPA 1998c).

The recent evaluations conducted by OW concluded that protecting against chloroform's noncancer health effects protects against excess cancer risk. EPA now believes that the noncancer health effects resulting from inhalation of chloroform would precede the development of cancer and would occur at lower doses than tumor development. Although EPA has not finalized a noncancer health benchmark for inhalation exposure (i.e., an RfC), ATSDR has developed an inhalation MRL for chloroform. Therefore, ATSDR's chronic inhalation MRL for chloroform (0.1 mg/m^3) was used in IWAIR.